Physiology | Lecture 10

Microcirculation & Edema Pt.2

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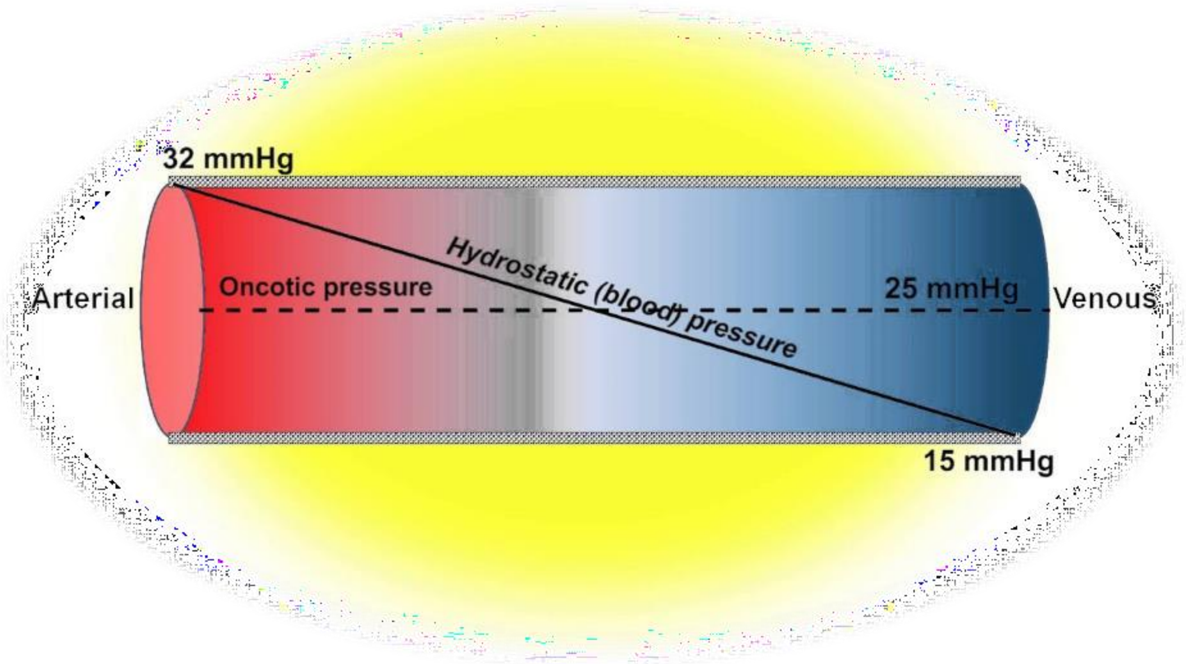
Introduction to Physiology

Final Exam Material

Dr. Yanal Shafagoj

Lecture 4

“Microcirculation and Edema”



Comprehensive File

What are the factors that lead to formation of edema?

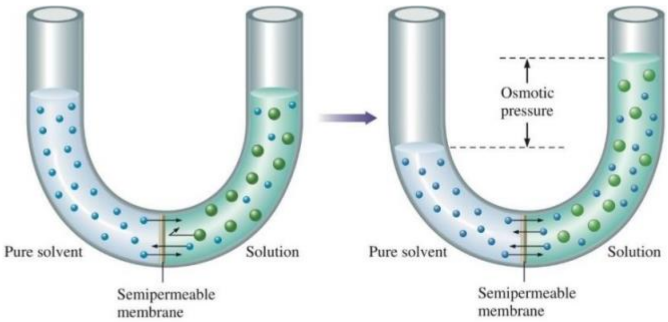
In this lecture we will continue talking about the 4 starling forces.

A) Hydrostatic pressures (due to fluid volume):

1. Blood hydrostatic pressure (BHP or P_c) is a force which favors filtration and opposes reabsorption.
2. Interstitial fluid hydrostatic pressure (IFHP or P_{IF}) is a force which opposes filtration and favors reabsorption. This is true if P_{IF} is +ve such as in Bowman's capsule in the kidney, but if it is -ve it will favor filtration such as in the lung.

B) Colloid Osmotic pressures (due to the presence of large proteins such as albumin and globulin):

3. Blood colloid osmotic pressure (BCOP or Π_c) is a force which opposes filtration and favors reabsorption.
4. Interstitial fluid osmotic pressure (IFOP or Π_{IF}) is a force which favors filtration and opposes reabsorption. In the lungs, it is 14 mmHg. (the interstitial colloid (oncotic) pressure is usually 8mmHg). **Interstitial protein concentration differs between tissues.**



This membrane is permeable to water but not to these solutes (let us assume that these solutes are proteins). The water diffuses from left to right (low to high osmolarity); this process is called osmosis.

As time passes, the height will increase in the right compartment and decrease in the left one due to osmosis.

Finally, the hydrostatic pressure will prevent net diffusion toward right when it become equal to the osmotic pressure (when talking about proteins as solutes we name this pressure collide osmotic pressure) it is directly proportional to ΔC (C: osmolarity)

The doctor didn't talk about what is colored in grey in details (read only)

The Vant Hoff Equation

Osmotic pressure = n x (c/M) x RT

The osmotic pressure (Π; capital π) is determined by 5 factors:

$\Pi = \sigma nRTC$

σ: reflection constant; ranges *from* 0 *to* 1; how much it is reflected

0 → completely permeable (not reflected from the membrane)

1 → impermeable (totally reflected)

n: dissociation constant; the # of particles resulting from the dissociation

for glucose (not ionic), n=1; for NaCl, n=2; for C aCl_2, n=3…

R: ideal gas constant

T: absolute temperature (in Kelvin)

C: molar concentration (before dissociation if present)

1 mOsm/L (of any plasma protein) yields 19.3 mmHg of osmotic pressure. Total concentration of proteins in the plasma is 6 – 8 g/dL. (almost only globulin and albumin)

The blood colloid osmotic pressure in the capillary ≈ 28 mmHg.

We refer to proteins when talking about Π since they have a very low permeability (very high σ) → strong effect on Π. Other particles such as ions (Na^+, K^+, Cl^-, Ca^{2+}…) and small molecules such as glucose do not contribute to Π due to their equal concentrations on both sides of the capillary wall. (you don't have to know about σ, just know the permeability)

The osmotic pressure in blood plasma is determined mainly by 2 proteins:

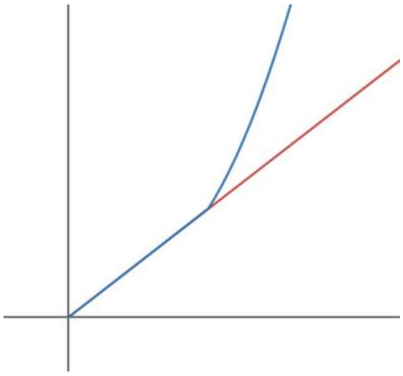
Protein	Concentration in capillaries	Molecular weight	Contribution to Π_c
Albumin	3.5 - 5.5 g/dL	70,000 g/mol	22 mmHg
Globulin	2 - 4 g/dL	140,000 g/mol	6 mmHg

Albumin is produced by the liver (albu means white)

Albumin is more important than globulin for Π_c due to 2 reasons:

1. Higher mass per liter (nearly 1.5 of the globulin's mass)
2. Lower molecular weight → more particles for a given mass. (More important than 1)

Because albumin is the dominant factor in determining Π, the osmotic pressure grows linearly with the concentration of albumin, but after a critical concentration, a small change in albumin's concentration will yield a huge change in Π.



X-axis: Albumin concentration; Y-axis: Osmotic pressure.

Red: Expected osmotic pressure after critical concentration – linear.

Blue: Real osmotic pressure after critical concentration – non-linear.

It is believed that after this critical concentration, albumin (due to its negative charge) will attract cations leading to increased particles and thus increased osmolarity → increased Π.

Suppose that albumin concentration is 4 g/dL which is equal to 40 g/L.

Let's calculate the molarity.

$$Molarity\ [\frac{mol}{L}] = \frac{concentration\ [\frac{g}{L}]}{molecular\ weight\ [\frac{g}{mol}]}$$

$$= \frac{40\,\frac{g}{L}}{70{,}000\,\frac{g}{mol}} = 0.0006\frac{mol}{L} = 0.6\frac{mmol}{L}$$

Since albumin does not dissociate, the osmolarity will be equal to the molarity

So, the albumin osmolarity is 0.6 mOsm/L.

As mentioned before, each mOsm/L yields 19.3 mmHg of Π. Theoretically, 0.6 mOsm/L will yield about 12 mmHg.

This contradicts the data in the table above which is 22 mmHg.

As we said before, the relation between Π and the concentration of albumin is not linear but shifts upward after a critical concentration. This explains why we have a higher value for Π than expected.

Capillary exchange

Almost all fluid in the interstitium is in the form of *gel* (fluid proteoglycan mixtures); there is a very little amount of free fluid under normal conditions.

Note: Blood hydrostatic pressure (Pc)= Force (which is exerted from the fluid on the walls of the capillaries; it depends on the volume of the plasma)/Area. Capillaries don't have smooth muscle cells that could constrict or dilate; the area remains constant. On the other hand, Constriction of venules makes (Pc) bigger, and dilation of arterioles also makes (Pc) bigger (V increases-> F increases).

There are 3 ways by which capillary exchange – movement of substances between blood and ISF – occurs.

1. Diffusion (most important for solute exchange):

Diffusion is the random movement of particles, and net diffusion is determined by the concentration gradient (higher to lower).

O_2 and essential nutrients move: blood in capillaries → ISF → body cells.

CO_2 and wastes move: body cells → ISF → blood in capillaries.

In the blood-brain barrier, tight junctions limit diffusion because it prevents the paracellular pathway.

-O_2 and CO_2 pass biological membranes as if they do not exist

-CO_2 passes 20 times faster than O_2

In general, large molecules such as proteins cannot cross the capillaries.

In some places, sinusoids, proteins and even blood cells can cross the capillaries.

2. Transcytosis:

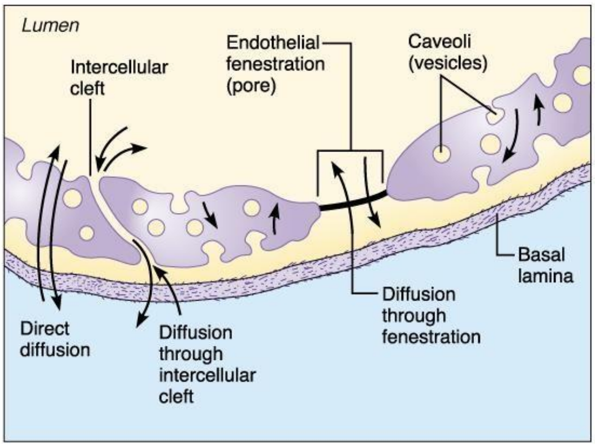
It is the transport of large molecules that cannot cross capillary walls, and it uses both endocytosis (on one end) and exocytosis (on the other end).

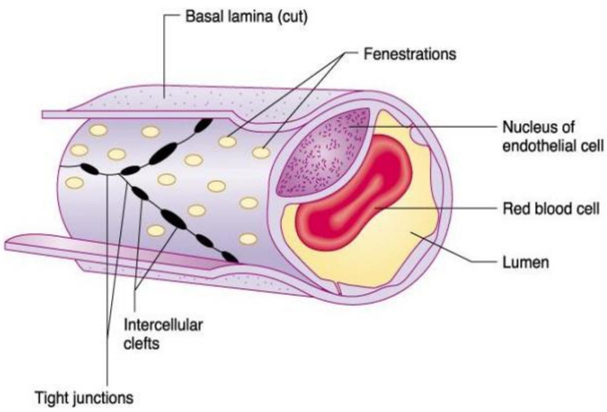
3. Bulk flow (or simply flow; most important for regulation of relative

volumes of blood and the ISF):

a. Passive process in which large numbers of ions, molecules, or particles in a fluid move together in the same direction.
b. Based on pressure gradient (starling forces).

In general, solutes and water move across capillary wall via intercellular cleft (space between cells) or through fenestrations (pores in the endothelial lining of the capillaries) or by plasmalemma vesicles (in transcytosis).





Interstitial protein concentration is different among different tissues.

Flow

The **flow** of fluids is determined by the sum of the 4 starling forces:

NFP (net filtration pressure) = filtration forces – reabsorption forces

$$Flow = [(filtration\ forces) - (reabsorption\ forces)] * K$$

$$Flow = [(P_c + \Pi_{IF}) - (P_{IF} + \Pi_c)] * K; K\ is\ the\ permeability$$

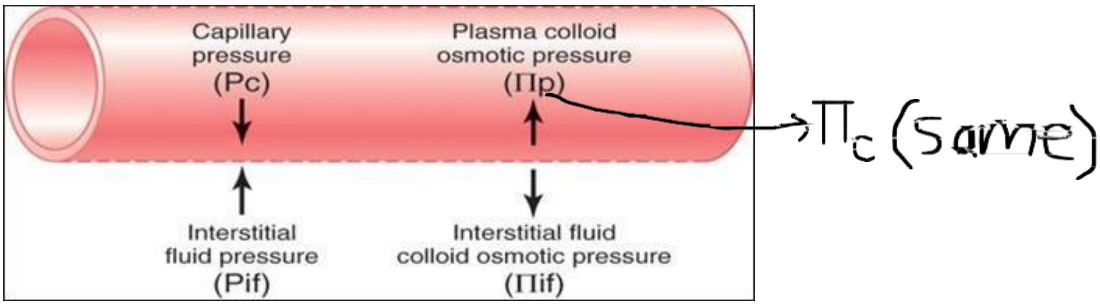
NFP = -NRP (net reabsorption pressure)
In the kidney we use NFP
in the intestine we use NRP

Refer to the top of page 1 for the definitions of the 4 forces.

Since we are using NFP, the following sign convention must be used:

If the flow is positive → filtration occurs.

If the flow is negative → reabsorption occurs.



- Example: in pulmonary capillaries , Pc= +10, Πc= +28 , Pi=-5, Πi=14

(Pc + Πi) – (Pi+ Πc) = (10+14) – (-5+ 28) = +1

The net force is positive which means filtration occurs.

Now if Pc in the previous example was +30, the net force will be:

(30+14)-(-5+28)= +21

This means that filtration will occur at very high rates but Edima would still not occur because of the high amount of lymphatic vessels in the lungs

Note: the lungs are full of lymphatic vessels to remove excess fluids that accumulate from the filtration process so that edema does not occur, because pulmonary edema is fatal.

Note: the lungs must be kept dry, there shouldn't be much filtration there and it should go back from wet to dry lungs quickly after filtration.

Starling's Law

3 of the 4 forces usually have constant values along the same capillary, however P_c has a varying value depending on the location along the capillary.

On the arterial end of the capillary, P_c is high (in skeletal muscles 40 mmHg), and on the venous end, P_c is lower (in skeletal muscles 20 mmHg).

On the arterial end, the sum of forces favoring filtration is higher than the ones favoring reabsorption due to the high value of P_c and thus filtration occurs (positive value for the flow in the equation).

On the venous end, the sum of forces favoring filtration becomes lower than the ones favoring reabsorption due to the relatively lower value for P_c and thus reabsorption occurs (negative flow).

This explains the behavior of ideal capillaries (such as in skeletal muscles).

Read only

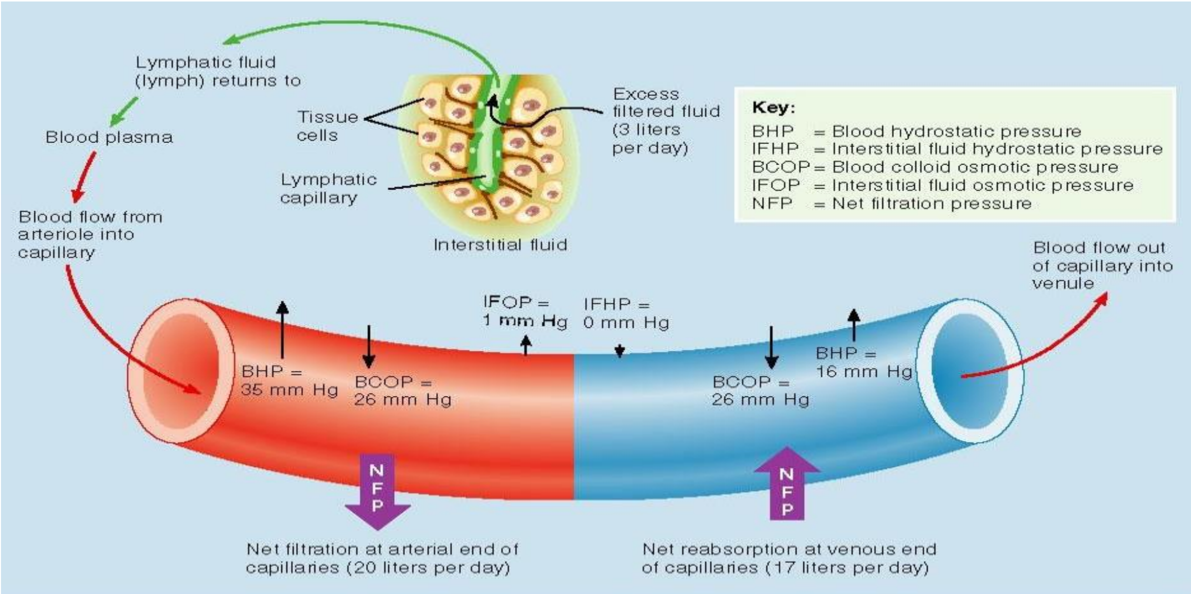
About 85% of the fluid filtered at the arterial end is reabsorbed at the venous end.

The leftover (15%) enters lymphatic capillaries to return to the blood.

P_{IF} (Interstitial fluid hydrostatic pressure) is usually close to zero (negligible) and could be slightly negative due to the pumping of the lymphatic system.

When it is negative, P_{IF} favors filtration instead of reabsorption.

Quantitative example:



Net filtration pressure (NFP) = (BHP + IFOP) − (BCOP + IFHP)

(BHP + IFOP): Pressures promoting filtration

(BCOP + IFHP): Pressures promoting reabsorption

	Arterial end	Venous end
	NFP = (35 + 1) − (26 + 0) = 10 mm Hg	NFP = (16 + 1) − (26 + 0) = − 9 mm Hg
Result	Net filtration	Net reabsorption

As we can see, net filtration pressure at the arterial end is +10 mmHg while net filtration pressure at the venous end is -9 mmHg (reabsorption occurs at the venous end because the NFP is negative).

The net force is [(+10) + (-9)] = +1 which means that net filtration occurs.

Note: pressure values may differ according to tissue type.

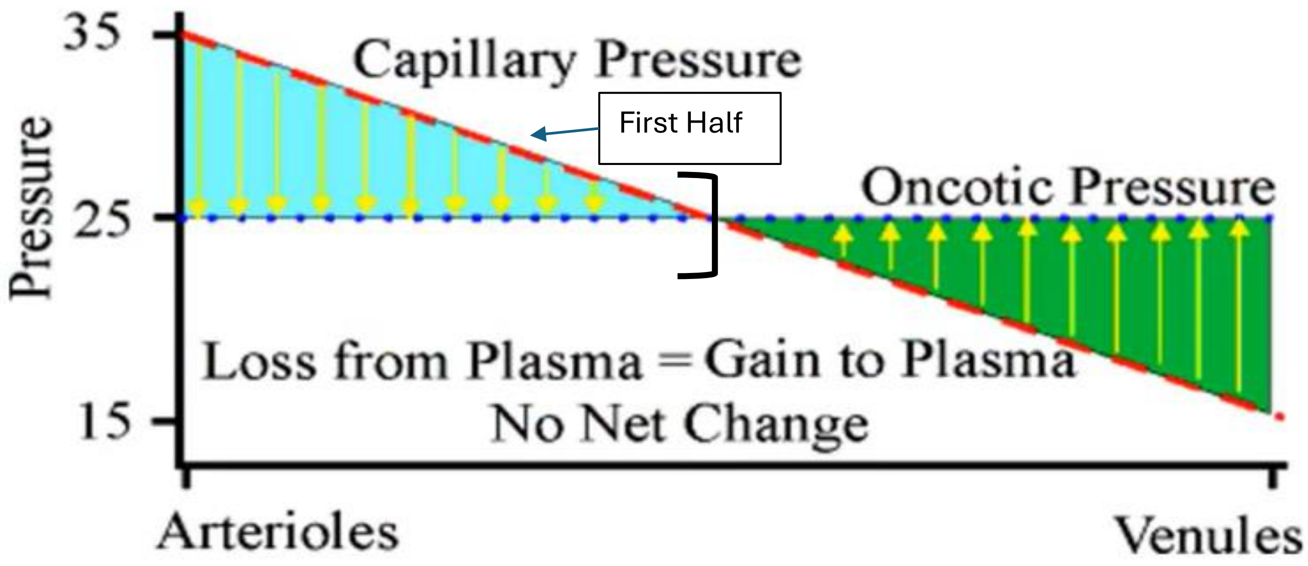
Another example:

Mean forces tending to move fluid outward (filtration):	
Mean Capillary pressure	17.3
Negative interstitial free fluid pressure	3.0
Interstitial fluid colloid osmotic pressure	8.0
Total outward force	28.3
Mean force tending to move fluid inward (reabsorption):	
Plasma colloid osmotic pressure	28.0
Total inward force	28.0
Summation of mean forces:	
Outward	28.3
Inward	28.0
Net force	+0.3 (outward; filtration)

In this example, we used the mean value for P_c between the arterial and venous ends. This calculation gives us the net force in one step instead of calculating the net force for each side then adding both values.

Since the net force is positive, we have net filtration occurring.

To calculate the flow, we multiply the net force (+0.3 mmHg) by the permeability (K).



On the arteriole end, the hydrostatic pressure is higher than the oncotic, so there is fluid movement from plasma to interstitium. The magnitude of this water flow is indicated by the light blue area on the left (downward arrows). On the venule end, the hydrostatic pressure has dropped below the oncotic pressure. Fluid moves back from the interstitium to the plasma. The magnitude of this reverse flow is indicated by the green area on the right (upward arrows).

There is no net filtration in this case.

In the first half, the capillary is losing fluid to the interstitium(filtration), while in the latter half the capillary is gaining fluid from the interstitium(absorption). However, the oncotic pressure is stable throughout the whole process (keep in mind that the oncotic pressure (Π) depends on Delta C which is -*delta C*- affected by the volume of fluid itself) even though one of its factors changed. So the reason why the oncotic pressure didn't change is because the amount of fluid that is either absorbed or filtered is **negligible.**

Experimentally, the net filtration rate is calculated to be **3L/day,** which we have discussed in the previous lecture as the filtered fluid flow (20 L/day) minus the reabsorbed fluid flow (17 L/day).

Filtration in the capillaries is approximately 20L/day and around 180L/day in the capillaries in kidneys given that both weigh only 250 grams.
The reason as to why kidneys' filtration is this high is that Pc is +60 and the permeability (K) of the capillary cells is high due to fenestrations(pores).

As a result of high filtration in the kidneys, the oncotic pressure in the plasma becomes 32 (28 when entering from afferent arteriole and 36 when exiting from efferent arteriole).

To make it clear, kidneys lose a lot of water during filtration (20% of the water in plasma whereas in other capillaries in the body only 0.5% is lost during filtration which is negligible), so a factor of concentration has greatly changed, which is the volume, hence, oncotic pressure has changed as well.
(**total number** of protein molecules hasn't changed at all)
(only in sinusoids proteins can cross the capillaries to interstitial and vice versa)

Oncotic pressure in the interstitial (bowman's space) of the kidney is **zero (3 starling forces not 4)** as it is highly impermeable to proteins (but highly permeable to other things).

A high driving force in the glomerular capillaries x high permeability =180L/day

A summary of pressures to memorize:

Capillary type	Glomerular	Pulmonary	Skeletal muscle
Πc/Πi mmHg	32 (28 near to the afferent arteriole 36 near to the efferent arteriole) /0	28/14	28/5
Pc/Pi mmHg	+60/+18	+10/-5	+30/0

P can be +/-/0 (zero means atmospheric pressure, at sea level 760mmHg)

Π can be +/0 only

Causes of Edema

1) increased P_c.
2) Decreased Π_c.

The normal albumin concentration range is from 3.5 – 5.5

g/dL. If it falls below 3.5 g/dL → hypoalbuminemia.

If it rises above 5.5 g/dL → hyperalbuminemia.

One of the causes of edema is hypoalbuminemia which is caused by the low concentration of albumin in the plasma.

This leads to decreased Π_c causing more filtration.

Causes of hypoalbuminemia:

a. Malnutrition (low intake of albumin).
b. Malabsorption in the intestines (low absorption).
c. Increased loss of albumin from the body in kidneys (albuminuria) due to glomerular nephritis.
d. Malproduction of albumin by the liver (liver cirrhosis or fibrosis –the introduction to cirrhosis- due to alcohol or hepatitis B or C) the decrease in the albumin of the blood is an indication of fibrosis or cirrhosis.

3) Lymphatic capillary blockage:

Excess interstitial fluids are not absorbed by lymphatic capillaries.

This causes the accumulation of fluids in the interstitial space → edema.

4) Leaking capillary wall:

Increase in the permeability (K) which can be caused by the release of histamine during allergic reactions such as after a bee sting.

There are a lot of lymphatic vessels in the pulmonary interstitium as it reabsorbs fluids and sends them back to the blood to keep the lungs dry to prevent life threatening edema. (edema safety factor)

- Hypoalbuminemia is a generalized edema because albumin will decrease in all of our blood (in all capillaries).
- Edema in lower limbs for pregnant women due to the constriction of femoral veins as the uterus increases in size and is a localized edema.
- The edema which can be caused by the release of histamine during allergic reactions such as after a bee sting is also localized edema (unless it causes anaphylaxis)

رسالة من الفريق العلمي:

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